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Identification of cysteine-rich domains of the type 1 tumor necrosis factor receptor involved in ligand binding.

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The extracellular portion of the type 1 (p55) and type 2 (p75) tumor necrosis factor (TNF) receptors contains a repetitive amino acid sequence pattern of four cysteine-rich domains (CRDs). This pattern is found also in several other cell surface proteins, including the p75 nerve growth factor receptor and the CD40, 4-1BB, OX40, Fas, and CD27 antigens. To investigate whether CRDs play a role in TNF binding, we have constructed soluble variants of the extracellular portion of human type 1 TNF receptor (sTNFR1), in which CRD1 (N-terminal) or CRD4 (C-terminal) was deleted by mutagenesis. These variants or a wild type sTNFR1 were linked in their C terminus to the hinge and Fc portion of IgG1 heavy chain to create sTNFR1-IgG chimeras (immunoadhesins). Deletion of either CRD1 or -4 did not cause any major perturbations in the structure of the sTNFR1 variants, as evidenced by their efficient expression and secretion from transfected cells, and by their binding to conformation-dependent monoclonal antibodies that recognize diverse epitopes on sTNFR1. The wild type sTNFR1 immunoadhesin exhibited high affinity binding to TNF alpha ($K_d = 65$ pM) and TNF beta ($K_d = 640$ pM). Deletion of CRD4 resulted in about a 10-fold reduction in affinity for TNF alpha ($K_d = 660$ pM) and for TNF beta ($K_d = 5.7$ nM). In contrast, deletion of CRD1 resulted in a complete loss of binding to TNF alpha and to TNF beta. These results indicate that CRD4 is important but not necessary for TNF binding, while CRD1 is required. In addition, the results suggest some overlap between the TNFR1 binding sites for TNF alpha and TNF beta, despite low amino acid sequence homology between these cytokines.

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